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APPLICATION NO	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO	CONFIRMATION NO
09/954,679	09/12/2001	Donna T. Ward	RTS-0212	7534

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Jane Massey Licata
Licata & Tyrrell, P.C.
66 East Main Street
Marlton, NJ 08053

EXAMINER
LACOURCIERE, KAREN A

ART UNIT	PAPER NUMBER
1635	

DATE MAILED: 06/04/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

FILE COPY

Application No.	Applicant(s)
09/954,679	WARD ET AL.
Examiner	**Art Unit**
Karen A. Lacourciere	1635

Office Action Summary

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *25 March 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,2 and 4-20* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2 and 4-20* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a)☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1)☒ Notice of References Cited (PTO-892)
2)☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3)☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s). *3*.
4)☐ Interview Summary (PTO-413) Paper No(s). _____.
5)☐ Notice of Informal Patent Application (PTO-152)
6)☐ Other:

DETAILED ACTION

Election/Restrictions

Applicant's amendments filed 03-25-2003 have obviated the restriction requirement set forth in the prior Office action, mailed 03-05-2003.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 18 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 18 recites the limitation "the disease or disorder". There is insufficient antecedent basis for this limitation in the claim, because it depends from claim 16, which recites a disease or condition.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 15-20 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of inhibiting the expression of ribonuclease L in cells and tissues in vitro (cell culture) using antisense targeted to a nucleic acid encoding ribonuclease L (SEQ ID NO:3), does not reasonably provide enablement for a method of inhibiting the expression of ribonuclease L in cells or

tissues in vivo (whole organism), a method of treatment or a method of modulating RNA interference using an antisense targeted to a nucleic acid encoding ribonuclease L. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

The following factors have been considered in formulating this rejection (*In re Wands*, 858F.2d 731, 8 USPQ2d 1400 (Fed. Cir. 1988)): the breadth of the claims, the nature of the invention, the state of the prior art, the relative skill of those in the art, the predictability or unpredictability of the art, the amount of direction or guidance presented, the presence or absence of working examples of the invention and the quantity of experimentation necessary.

Claims 15-20 are drawn broadly to inhibition of the expression of ribonuclease L in any cell *in vivo* (whole organism) for the treatment of any disease that is associated with ribonuclease L, including treating any disease or condition resulting from an infection, any disease or condition associated with ribonuclease L that is the result of aberrant apoptosis, or any cancer using antisense targeted to a nucleic acid encoding ribonuclease L.

The specification provides examples wherein chimeric phosphorothioate antisense targeted to a nucleic acid encoding ribonuclease L inhibited the expression ribonuclease L *in vitro* (cell culture) in human cell lines. The specification does not demonstrate any correlation with the inhibition of ribonuclease L in cell culture and a treatment effect for any disease or condition associated with ribonuclease L. The

specification does not present any examples wherein antisense targeted to ribonuclease L was delivered to cells *in vivo* (whole organism), nor wherein antisense targeted to ribonuclease L inhibited the expression of ribonuclease L in cells *in vivo* (whole organism). The specification does not provide any examples wherein treatment effects were obtained for any disease or condition, including an infection or a disease or condition resulting from aberrant apoptosis or cancer using antisense targeted to ribonuclease L. The specification does not demonstrate modulating the expression of ribonuclease L using antisense, only inhibiting of ribonuclease L. The specification does not demonstrate modulating RNA interference using antisense targeted to ribonuclease L, or ihbiting or increasing RNA interference using antisense to ribonuclease L. The specification does not demonstrate that ribonuclease L is associated with RNA interference, nor does the art recognize its involvement.

The specification does not present any guidance on what specific diseases or conditions can be treated using antisense targeted to ribonuclease L including specific infection, cancers or conditions which arise from aberrant apoptosis, and what cells to target for a particular disease or condition.

At the time the instant invention was made, the therapeutic use of antisense oligonucleotides was a highly unpredictable art due to obstacles that continue to hinder the therapeutic application of antisense *in vivo* (whole organism) (see for example Agrawal et al. (Molecular Medicine Today, Vol 6, p 72-81, February 2000), Branch (TIBS 23, Feb 1998, p45-50), Green et al. (J. Am Coll. Surg., Vol 191, No. 1, July 2000, p 93-105), Jen et al. (Stem Cells 2000, Vol. 18, p 307-319)). Such obstacles include,

for example, problems with delivery, target accessibility and the potential for unpredictable nonantisense effects. Jen et al. state (see page 313, second column, second paragraph) "One of the major limitations for the therapeutic use of AS-ODNs and ribozymes is the problem of delivery....Presently, some success has been achieved in tissue culture, but efficient delivery for *in vivo* animal studies remains questionable". Jen et al. outlines many of the factors limiting the application of antisense for therapeutic purposes and concludes (see p 315, second column), "Given the state of the art, it is perhaps not surprising that effective and efficient clinical translation of the antisense strategy has proven elusive."

Green et al. state, "It is clear that the evolution of antisense technology from a laboratory research tool into a mechanism for designing active and effective drugs is far from complete. Although there is little doubt that systemically administered antisense ODNs can inhibit the expression of specific genes in patients, the effectiveness of such therapy in modifying the course of a particular illness has not yet been established....Clearly, additional work must be done to unravel the complex problems associated with drug delivery, mRNA targeting and aptameric, nonantisense effects."

Given this unpredictability, the skilled artisan would require specific guidance to practice the claimed methods *in vivo*, with a resultant therapeutic outcome, as claimed. The specification provides examples wherein antisense is delivered to cells *in vitro* and the expression of ribonuclease L is inhibited, however, cell culture examples are generally not predictive of *in vivo* inhibition due to differences in metabolites and clearance rates, local concentration of antisense, differences in target site accessibility,

cellular uptake differences and the potential for non-antisense side effects. Often formulations and techniques for delivery *in vitro* (cell culture) are not applicable *in vivo* (whole organism) (see for example Jen et al., page 313, second column, second paragraph). For example, Agrawal et al. (see p 79-80, section entitled *Cellular uptake facilitators for in vitro studies*) states "The cellular uptake of negatively charged oligonucleotides is one of the important factors in determining the efficacy of antisense oligonucleotides.....In vitro, cellular uptake of antisense oligonucleotides depends on many factors, including cell type, kinetics of uptake, tissue culture conditions, and chemical nature, length and sequence of the oligonucleotide. Any one of these factors can influence the biological activity of an antisense oligonucleotide." Due to differences in the physiological conditions of a cell *in vitro* versus *in vivo*, the uptake and biological activity observed *in vitro* would not predictably translate to *in vivo* results.

The field of antisense, to date, does not provide guidelines by which antisense can be routinely delivered to generally any cell type *in vivo* (whole organism) at a concentration effective to result in a predictable therapeutic effect. The specification does not provide specific guidance by which one skilled in the art would expect to be able to deliver antisense targeted to ribonuclease L to generally any target cell or tissue *in vivo* (whole organism) at a concentration effective to provide a pharmaceutical effect or to treat the broad range of diseases encompassed by the claims or to modulate RNA interference, particularly wherein the claims specify a pharmaceutically effective amount.

In order to practice the invention claimed, over the full scope claimed, one skilled in the art would need to undergo undue trial and error experimentation, beyond the teachings of the instant specification. The quantity of undue experimentation would include the determination of what specific diseases and conditions can be treated by the inhibition of the expression of ribonuclease L, what specific cells to target with ribonuclease L antisense for the treatment of a particular disease or condition, and how to specifically deliver antisense to a target cell *in vivo* (whole organism) at a concentration effective to result in inhibition of the expression of ribonuclease L to a level sufficient to result in a pharmaceutical effect or to treat a disease. The skilled artisan would need to determine if RNA interference can be modulated using ribonuclease L antisense and is unlikely to be able to do so, given that each antisense disclosed in the specification inhibits ribonuclease L and it is unclear that ribonuclease L is even associated with the RNA interference pathway. Additionally, this undue experimentation would include the determination of such factors as dosage, route of administration, disposition of the antisense molecule in tissues, and the half life and stability of the antisense molecule *in vivo*. Given the art recognized unpredictability of the therapeutic application of antisense *in vivo* (whole organism), this determination would not be routine and would require undue trial and error experimentation.

Therefore, due to the broad scope of the methods of treatment claimed and the in vivo modulation claimed, the state of the art of antisense, the level of unpredictability of *in vivo* (whole organism) methods of treatment using antisense, the lack of specific guidance for the *in vivo* (whole organism) application of antisense methods of treatment

and the lack of working examples or examples which correlate with the claimed methods, one skilled in the art would not be able to practice the methods of claims 15-20 over the full scope claimed without undue trial and error experimentation.

Claim Rejections - 35 USC § 102 or 35 USC § 103

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1, 2 and 11 are rejected under 35 U.S.C. 102(b) or 35 USC 103(a) as being anticipated by or obvious over Ogawa et al. (WO 96/38034).

Ogawa et al. (WO 96/38034) disclose a 35-mer oligonucleotide that is fully complementary to SEQ ID NO:3 (see page 22, second sequence listed for RNaseL). Ogawa et al. was not available in English at the time this Office action was prepared,

however, the claims have only been rejected on the basis of sequence information. The oligonucleotide disclosed by Ogawa et al. meets all of the structural requirements of the instant claims, the oligonucleotides would also be expected to specifically hybridize to nucleic acid encoding ribonuclease L, as per applicant's definition set forth in the specification as filed, page 10, lines 6-10.

Furthermore, since the prior art oligonucleotides meet all the structural limitations of the claims, the prior art oligonucleotides would then be considered to "inhibit expression" of the gene as claimed, absent evidence to the contrary. See, for example, MPEP § 2112, which states "[w]here applicant claims a composition in terms of a function, property or characteristic and the composition of the prior art is the same as that of the claim but the function is not explicitly disclosed by the reference, the examiner may make a rejection under both 35 U.S.C. 102 and 103, expressed as a 102/103 rejection. 'There is nothing inconsistent in concurrent rejections for obviousness under 35 U.S.C. 103 and for anticipation under 35 U.S.C. 102.' In re Best, 562 F.2d 1252, 1255 n.4, 195 USPQ 430, 433 n.4 (CCPA 1977). This same rationale should also apply to product, apparatus, and process claims claimed in terms of function, property or characteristic. Therefore, a 35 U.S.C. 102/103 rejection is appropriate for these types of claims as well as for composition claims."

Therefore, the instant invention is anticipated or obvious over Ogawa et al. (WO 96/38034).

Claims 1, 2, 11, 12 and 14 are rejected under 35 U.S.C. 102(b) or 35 USC 103(a) as being anticipated by or obvious over Ogawa et al. (US 6,320,099).

Ogawa et al. (US 6,320,099) disclose a 35-mer oligonucleotide that is fully complementary to SEQ ID NO:3 (see SEQ ID NO 8, column 16, second primer for RNaseL). Ogawa et al. disclose their oligonucleotide in a composition comprising a pharmaceutically acceptable carrier (eg. water). The oligonucleotide disclosed by Ogawa et al. is disclosed as a primer, however, the oligonucleotide meets all of the structural requirements of the instant claims, the oligonucleotides would also be expected to specifically hybridize to nucleic acid encoding ribonuclease L, as per applicant's definition set forth in the specification as filed, page 10, lines 6-10.

Furthermore, since the prior art oligonucleotides meet all the structural limitations of the claims, the prior art oligonucleotides would then be considered to "inhibit expression" of the gene as claimed, absent evidence to the contrary. See, for example, MPEP § 2112, which states "[w]here applicant claims a composition in terms of a function, property or characteristic and the composition of the prior art is the same as that of the claim but the function is not explicitly disclosed by the reference, the examiner may make a rejection under both 35 U.S.C. 102 and 103, expressed as a 102/103 rejection. 'There is nothing inconsistent in concurrent rejections for obviousness under 35 U.S.C. 103 and for anticipation under 35 U.S.C. 102.' In re Best, 562 F.2d 1252, 1255 n.4, 195 USPQ 430, 433 n.4 (CCPA 1977). This same rationale should also apply to product, apparatus, and process claims claimed in terms of function, property or characteristic. Therefore, a 35 U.S.C. 102/103 rejection is

appropriate for these types of claims as well as for composition claims."

Therefore, the instant invention is anticipated or obvious over Ogawa et al. (US 6,320,099).

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1, 2 and 4-15 are rejected under 35 U.S.C. 103(a) as being unpatentable over Maitra et al. (J. Virology Feb 1998, pages 1146-1152, reference AF on PTO form 1449, filed 09-12-2001) in view of Silverman et al. (US 6,028,243, reference AD on PTO form 1449, filed 09-12-2001), Zhou et al. (reference AL on PTO form 1449, filed 09-12-2001), Milner et al. and Barracchini et al.

Claims 1, 2 and 4-15 are drawn to an antisense compound 8-50 nucleotides in length targeted to a nucleic acid encoding ribonuclease L (SEQ ID NO:3), wherein the antisense comprises modified bases, including 5-methylcytosine modifications, modified sugars, including 2'-O-methoxyethyl modifications, internucleoside linkage modifications, including phosphorothioate, chimeric antisense, and compositions comprising said antisense and a pharmaceutically acceptable carrier, including a colloidal dispersion system. The claims are further drawn to methods to inhibit the expression of ribonuclease L in cells *in vitro*.

Maitra et al. teach antisense targeted to a nucleic acid encoding ribonuclease L expressed from a vector to inhibit the expression of ribonuclease L in cells in vitro. Maitra et al. do not teach antisense targeted to a nucleic acid encoding ribonuclease L of a length 8-50 nucleobases long. Maitra et al. do not teach antisense targeted to a nucleic acid encoding ribonuclease L wherein the antisense comprises a modified backbone, base or sugar, or chimeric antisense molecules.

Silverman et al. teach inhibiting the expression of ribonuclease L in cells using gene interruption to make a cell line useful to screen in vitro for antiviral drugs (see for example column 4).

Zhou et al. teach the full length sequence of a nucleic acid encoding ribonuclease L of SEQ ID NO:3.

Baracchini et al. teach 2'-O-methoxyethyl sugar modifications, 5-methyl cytosine base modifications, chimeric oligonucleotides and modified internucleoside linkages, including phosphorothioate linkages, to increase antisense stability and enhance affinity

and antisense oligonucleotides of 8-30 nucleotides in length. Baracchini et al. further teach pharmaceutical carriers and colloidal dispersion systems (for example liposomes) for use in delivery of antisense compounds.

Milner et al. teach methods of screening for determining antisense targeted to any known gene.

It would have been obvious to one of ordinary skill in the art to make an antisense molecule targeted to ribonuclease L because Maitra et al. teach that antisense is a viable means to inhibit the expression of ribonuclease L in cells in vitro and Silverman et al. teach that a cell line comprising an inhibition of ribonuclease L was useful as a tool to screen for antiviral drugs, in vitro. It would have been obvious to one of ordinary skill in the art to make an antisense oligonucleotide targeted to a nucleic acid encoding ribonuclease L, as taught by Maitra et al., of a length within the range of 8-50 nucleobases (as taught by Baracchini et al.), because antisense of a short length are more easily synthesized and easier to deliver to cells than a vector expressing a full length antisense and because this length was the convention in the art. It would have been further obvious to make said antisense comprising modifications, including 2'-O-methoxyethyl, 5-methyl cytosine, chimeric oligonucleotides and modified internucleoside linkages, including phosphorothioate linkages, as taught by Baracchini et al., because such modifications were routine and well known in the art as modifications which enhance the stability, uptake and affinity of an antisense molecule (see for example Baracchini et al. column 6, paragraph 3) and such benefits would have been useful in a cell line inhibited in vitro for drug screening purposes. It would have been obvious to

one of ordinary skill in the art to make a composition comprising said antisense and a pharmaceutically acceptable carrier, including a colloidal dispersion system, because pharmaceutically acceptable carriers, including colloidal dispersion systems (e.g. liposomes) were well known in the art for use with antisense molecules as a means to deliver antisense molecules to cells *in vitro* (cell culture), as evidenced by Baracchini et al.

One skilled in the art would have been motivated to make an antisense molecule targeted to a nucleic acid encoding ribonuclease L because Silverman teach inhibiting the expression of ribonuclease L for antiviral drug screening and antisense was a well known means for inhibiting the expression of a target molecule in vitro and Maitra et al. teach that antisense to inhibit ribonuclease L in cell in vitro. One of ordinary skill in the art would be motivated to make such antisense of a length within the range of 8-50 nucleobases for ease of synthesis and delivery and because it is conventional in the art to make antisense within this range (as exemplified by Baracchini et al.). One of ordinary skill in the art would have been motivated to incorporate the modifications taught by Baracchini et al. for the benefits of stability and improved hybridization.

One skilled in the art would have expected to be able to find antisense which inhibits the expression of ribonuclease L because the sequence of nucleic acids encoding ribonuclease L, including SEQ ID NO:3 were known in the art (see for example Zhou et al.) and methods of screening for antisense to a known gene was routine (see for example Milner).

It would have been obvious to one of ordinary skill in the art to use antisense targeted to a nucleic acid encoding ribonuclease L in a method of inhibiting the expression of ribonuclease L in cells *in vitro* (cell culture), because Maitra et al. teach using an expressed antisense targeted to ribonuclease L to inhibit the expression of ribonuclease L in cells *in vitro*, and it would be an obvious use for an antisense molecule designed to hybridize to and inhibit the expression of a nucleic acid encoding ribonuclease L.

Therefore, the invention of claims 1, 2 and 4-15 would have been obvious to one of ordinary skill in the art, as a whole, at the time the instant invention was made.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Karen A. Lacourciere whose telephone number is (703) 308-7523. The examiner can normally be reached on Monday-Thursday 8:30-6:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, John L. LeGuyader can be reached on (703) 308-0447. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 308-4242 for regular communications and (703) 305-1935 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

Karen A. Lacourciere
June 2, 2003

Karen A. Lacourciere
KAREN LACOURCIERE
PATENT EXAMINER